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TOLERANCE TO AND RESIDUAL EFFECTS OF COCAINE IN SQUIRREL MONKEYS DEPEND ON REINFORCEMENT-SCHEDULE PARAMETER

CHRISTINE E. HUGHES AND MARC N. BRANCH

UNIVERSITY OF FLORIDA

Lever pressing by 4 squirrel monkeys was maintained under a three-component multiple fixed-ratio schedule of food presentation; components differed with respect to ratio size. For each monkey, acute administration of cocaine (0.03 to 1.3 mg/kg, i.m.) produced dose-dependent decreases in overall response rate in each component. During repeated daily administration of 1.0 mg/kg of cocaine, tolerance developed to the rate-decreasing effects under each of the ratio contingencies, but developed to a greater extent and was evident in earlier parts of sessions for performance under the smaller ratios. Response rates of 2 monkeys increased above nondrug control levels despite the putative reinforcer not being consumed during the session. When saline or a smaller dose of cocaine was substituted for 1.0 mg/kg, response rates often were suppressed below nondrug control-level responding. This suppressive effect was observed in each monkey and was more likely to be observed and/or to be of greater magnitude in large-ratio components for 3 of the 4 monkeys. When saline was administered chronically at the end of the chronic-drug phase, response rates remained suppressed in the large-ratio component for 2 of the monkeys. There was, therefore, a schedule-dependent dissociation between behavioral tolerance and the residual effects: Tolerance was greater when small ratios were arranged, whereas the residual effects were more pronounced when larger ratios were arranged.

Key words: fixed-ratio schedules, cocaine, behavioral tolerance, behavioral hangover, multiple schedule, lever press, squirrel monkey

Most laboratory research on cocaine's effects on behavior has involved pigeons or rats (e.g., MacPhail & Seiden, 1975; Schama & Branch, 1989; Woolverton, Kandel, & Schuster, 1978). There is, however, a small body of research concerning cocaine's effects on nonhuman primates (e.g., Byrd, 1980; Johanson, 1978; Matsuzaki, Spingler, Misra, & Mulé, 1976; Post, Kopanda, & Black, 1976). In the examination of cocaine's effects on schedule-controlled behavior, fixed-ratio (FR) and fixed-interval (FI) schedules of reinforcement have been studied most frequently. Intermediate doses of cocaine (0.1 to 1.0 mg/kg) have increased overall response rates of squirrel monkeys' lever pressing maintained under multiple schedules in which FI 5-min schedules of either electric shock presentation, food presentation, or stimulus-shock termination alternated (Barrett, 1976; Branch, 1979). Larger doses decreased overall response rates. Similar results have been obtained under second-order FI 5-min (FR 30) schedules of food presentation (Gonzalez & Goldberg, 1977) and in the FI 10-min components of food presentation or stimulus-shock termination in multiple schedules comprised of FI 10-min and FR 30 components (Gonzalez & Goldberg, 1977; Spealman, Goldberg, Kelleher, Goldberg, & Charlton, 1977; Spealman et al., 1979). In the studies employing FI or FR schedules, doses that produced an increase in overall response rates in the FI components decreased overall response rates in the FR 30 components of multiple schedules of food presentation or stimulus-shock termination and in solitary FR 30 schedules of food presentation (Gonzalez & Goldberg, 1977; Spealman et al., 1977, 1979). The decreases in overall rates resulted from a decrease in the run rates and an increase in the postreinforcement pauses. In general, studies of cocaine's acute effects on behavior in nonhuman primates have yielded results that are consistent with those seen in other species (e.g., MacPhail & Seiden, 1975; Moore & Thompson, 1978; Woolverton et al., 1978).

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Research on effects of repeated cocaine administration on schedule-controlled behavior also has focused on species other than primates (e.g., Schama & Branch, 1989; Woolverton et al., 1978). A factor that has been shown to modulate the development of tolerance to the behavioral effects of cocaine in these studies is the schedule of reinforcement maintaining responding. For example, Hoffman, Branch, and Sizemore (1987) studied pigeons' key pecking maintained under a three-component multiple FR schedule of food presentation. Components differed with respect to the size of the ratio; values were 5, 25, and 125. Acute administration of cocaine produced dose-dependent decreases in response rates and reinforcement frequency under each schedule parameter, with performance during the FR 125 component being the most sensitive to the effect. Tolerance to these rate-decreasing effects was observed under the small and medium ratios, but not at all or to a lesser degree under the large ratio after daily administration of 5.6 mg/kg cocaine. Hoffman et al. pointed to the ratio of responses to reinforcer as a factor in the development of tolerance.

The present study was designed as a systematic interspecies replication of the Hoffman et al. (1987) study. Squirrel monkeys' lever pressing was maintained by a three-component multiple FR schedule of food presentation, and the effects of acutely and chronically administered cocaine were investigated. Cocaine, when administered acutely, typically produces overall decreases in response rates maintained by FR schedules of food presentation in both pigeons and squirrel monkeys (e.g., Gonzalez & Goldberg, 1977; Hoffman et al., 1987). Therefore, it was predicted that the differential development of tolerance as a function of FR size observed by Hoffman et al. in pigeons would also be observed with squirrel monkeys.

METHOD

Subjects

Four adult male squirrel monkeys (*Saimiri sciureus*), obtained from Primate Imports, served. They were housed individually in a colony room (12:12 hr light/dark) with free access to 0.1% vitamin-water solution (VI-DAYLIN® multivitamin drops, Ross Laboratories). They were maintained at 85% of their free-feeding weights through restricted postsession feeding of Purina® high protein monkey chow and, at least once weekly, fruit. Once food deprived, Monkeys 512, 514, 533, and 536 weighed 837, 874, 948, and 852 g, respectively. All monkeys had been studied previously under intermittent schedules of reinforcement and had received atropine and physostigmine. No drugs, however, had been administered for at least 9 months prior to the start of the present experiment.

Apparatus

Experimental sessions were conducted in a Plexiglas restraining chair similar in construction to that described by Hake and Azrin (1963). Subjects were restrained at the waist in a sitting position. A response lever (model E21-03, Coulbourn Instruments) was located on the right side of the Plexiglas panel facing the monkey. Static forces in excess of approximately 30 g (0.29 N) operated a switch attached to the lever, resulted in operation of a relay mounted near the base of the chair, and were counted as responses. Three pairs of 28-V colored lights were located above the lever in a horizontal row behind the Plexiglas wall. A Gerbrands Model D-1 pellet dispenser could deliver banana-flavored Noyes food pellets (190 mg) into a receptacle positioned to the left of the lever.

During sessions, the chair was placed in a sound-attenuating enclosure located in a room with white noise continuously present. A PDP-8/F® minicomputer in an adjacent room, operating under the SKED® process control system (Snapper & Inglis, 1978), programmed contingencies and collected data. A Gerbrands Model C-3 cumulative response recorder also was used to monitor responding.

Procedure

All subjects were trained to press the lever on a three-component multiple schedule of food presentation in which each component normally consisted of five consecutive repetitions of an FR schedule. The components differed with respect to ratio value. A small ratio value was correlated with illumination of a pair of white lights, a medium ratio value with a pair of green lights, and a large ratio value with a pair of red lights. Sessions began with a 5-min timeout, during which the lights were out and the lever was inoperative. After the timeout, one of the pairs of lights, randomly selected,

was turned on, and its associated FR was in effect. Completion of each FR resulted in delivery of one pellet and a 100-ms offset of the stimulus lights. After the fifth pellet delivery or the lapse of a time limit, a 60-s timeout occurred, and then the second component was randomly selected from the remaining two. The remaining component was then presented, following a 60-s timeout at the end of the second component. This process was repeated twice more; thus, each session consisted of three blocks of three components of the multiple schedule.

The time limits for each component were 2 min for the small-ratio component, 10 min for the medium-ratio component, and 20 min for the large-ratio component. These values were chosen such that they were at least twice as long as the longest duration of a component observed after stable responding had been established and before drugs were administered. If the time limit was reached without completion of the five FRs, the 60-s timeout occurred and the next component started.

Ratio values for the subjects were FR 5, FR 17, and FR 60 for M512 and M533; FR 5, FR 21, and FR 90 for M514; and FR 5, FR 25, and FR 125 for M536. The large-ratio values were selected through preliminary experiments so that responding under the large-ratio component was maintained throughout the session. Performance was not well maintained under larger ratios for M512, M514, and M533. The medium-ratio values were selected such that they were as proportionally larger than the small ratios as they were smaller than the large ratios. Sessions were conducted 7 days a week at approximately the same time each day.

Assessment of Acute Drug Effects

Drug experiments began after lever-pressing performance had become stable from session to session. Performance was considered stable after 10 consecutive sessions showed minimal variability and no consistent trends in response rates as determined by visual examination of the daily plots. This took 21, 12, 29, and 29 sessions for M512, M514, M533, and M536, respectively, once the final FR parameters had been selected. Cocaine hydrochloride (Sigma) was dissolved in 0.9% sodium chloride (saline) solution. Dosages were determined in terms of the salt. Injections, in a volume of 0.5 mL/kg, determined by the 85% free-feeding body weight (i.e., monkeys received the same volume every injection), were made in the thigh or calf muscle (site rotated from injection to injection) immediately prior to sessions. Dosages were administered in at least two ascending series: saline, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, and 1.3 mg/kg. Administrations were spaced at least 4 days apart.

Assessment of Chronic Drug Effects

After the assessment of the acute drug effects and at least 10 consecutive days of stable responding, subjects were given daily presession sham injections (needle inserted, no fluid injected). After 10 consecutive days of stable responding under the sham-injection routine, daily administration of 1.0 mg/kg cocaine commenced. This dose was selected because it reduced but did not eliminate responding in all components during acute administration; therefore, increases or decreases in the effects of this dose of cocaine could be observed. Injection location rotated, from session to session, from the left thigh, left calf, right thigh, and right calf to prevent bruising.

After at least 20 consecutive days of administration of 1.0 mg/kg cocaine, other dosages occasionally were substituted for the daily dosage and were administered in two ascending series: saline, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, and 1.3 mg/kg. These probe dosages were administered at least 4 days apart, with intervening sessions still preceded by injections of 1.0 mg/kg. For M536, two sets of probes (i.e., four ascending series) were conducted because of a shift in this subject's day-to-day performance shortly after completion of the first set. The chronic phase lasted 199, 111, 184, and 166 days for M512, M514, M533, and M536, respectively.

At the end of the series of daily cocaine administration, daily administration of saline began and continued for 10, 38, and 10 days for M512, M514, and M536, respectively. M536 was then exposed to the multiple schedule for an additional 55 sessions without injections prior to sessions. For reasons detailed below, M533 was exposed to several additional manipulations near the end of the series of daily cocaine injections. Saline was then administered before sessions for 15 days, after which M533 was exposed to the multiple schedule for an additional seven sessions without injections prior to sessions.

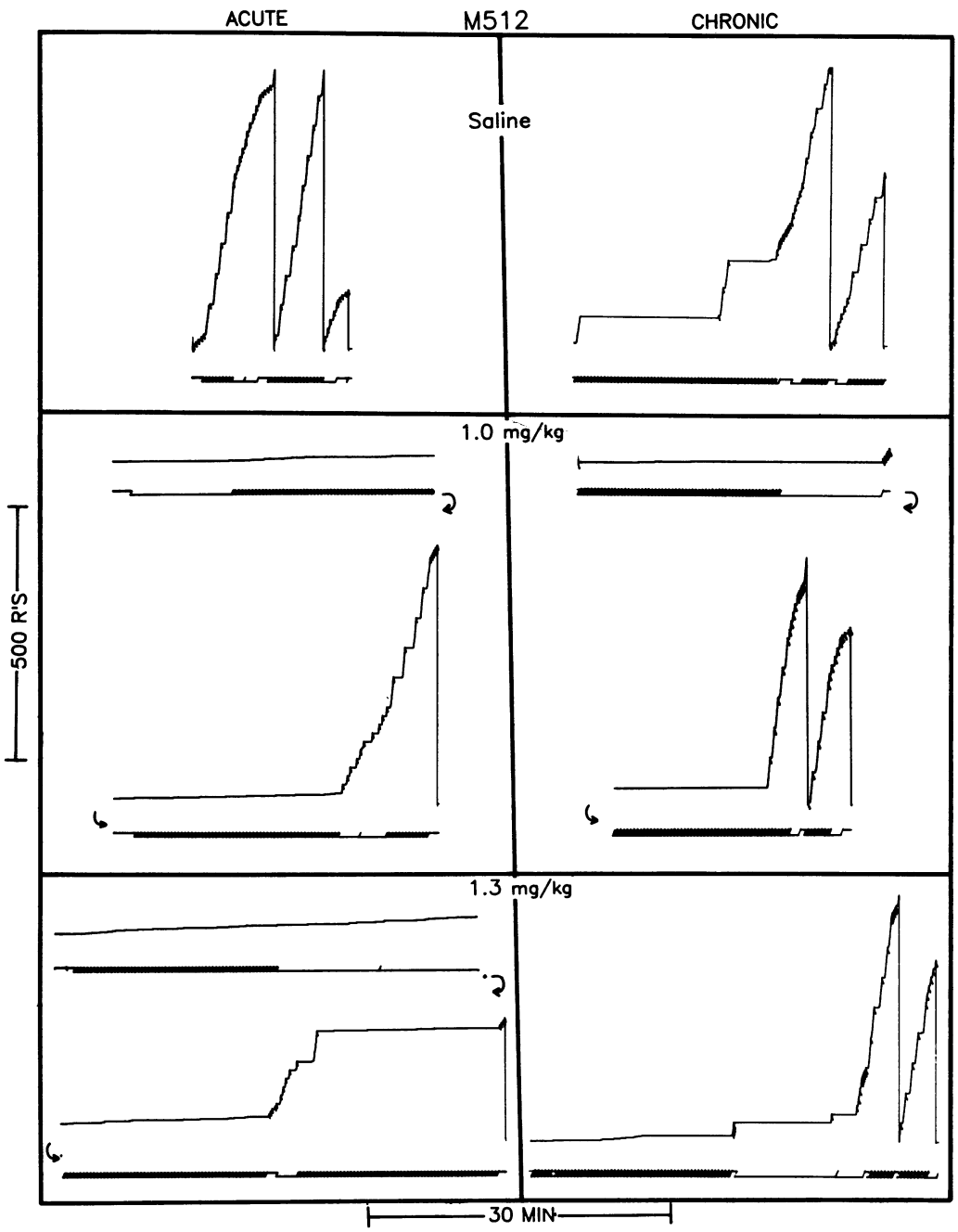

Fig. 1. Representative cumulative response records from M512 during acute (left panels) and chronic (right panels) administration. Performances following saline (top row), 1.0 mg/kg of cocaine (middle row), and 1.3 mg/kg of cocaine (bottom row) are shown. Downward deflections of the response pen indicate food delivery. Event pen (horizontal line below cumulative record) up indicates the FR 5 component, downward deflections indicate the FR 17 component, and alternating up-and-down deflections indicate the FR 60 component. The records in the middle and lower left panels have been broken to conserve space, with early-session responding illustrated in the top part of the panel and late-session responding shown in the lower part. Cumulative records in the right panels are from the 117th (saline), 180th (1.0 mg/kg), and 156th (1.3 mg/kg) sessions during daily administration of 1.0 mg/kg cocaine.

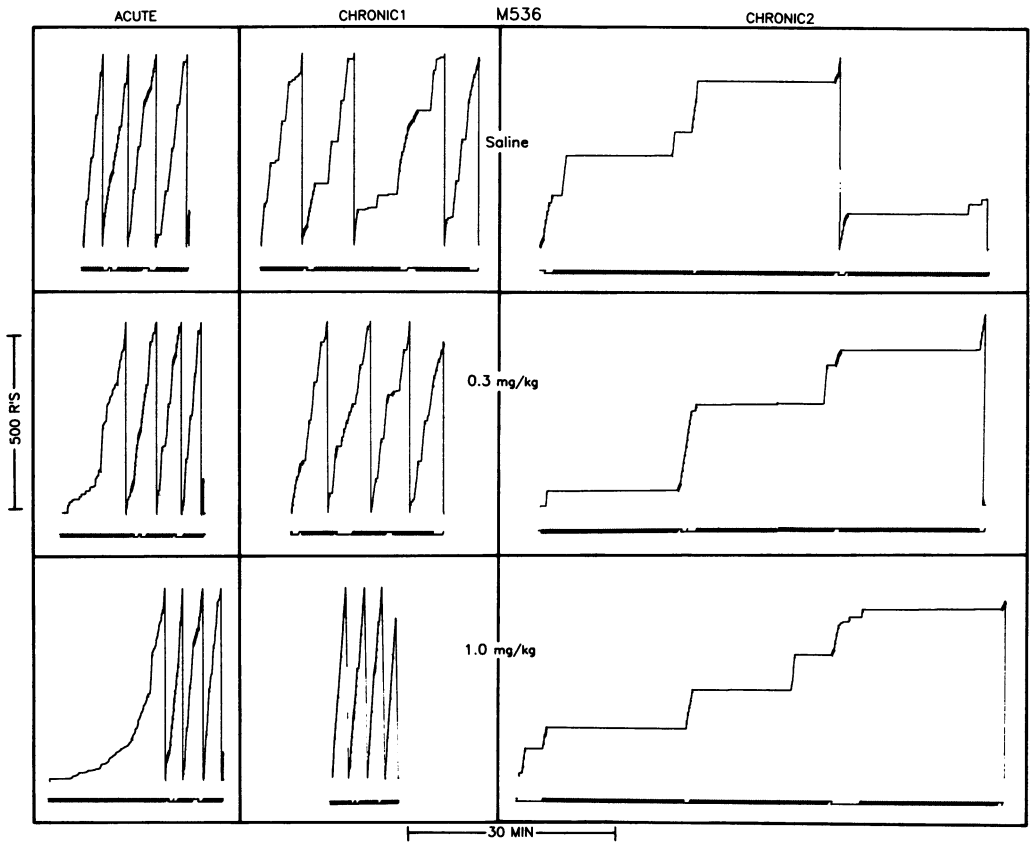

Fig. 2. Representative cumulative response records from M536 during acute (left panels), Chronic 1 (middle panels), and Chronic 2 (right panels) administration. See text for a description of the Chronic 1 and Chronic 2 phases. Performances following saline (top row), 0.3 mg/kg of cocaine (middle row), and 1.0 mg/kg of cocaine (bottom row) are shown. Recording conventions are the same as in Figure 1. Records in the middle panel are from the 55th (saline), 42nd (0.3 mg/kg), and 69th (1.0 mg/kg) sessions, and records in the right panel are from the 134th (saline), 109th (0.3 mg/kg), and 101st (1.0 mg/kg) sessions of daily administration of 1.0 mg/kg cocaine.

RESULTS

Acute Drug Effects

Figures 1 and 2 show cumulative response records of lever pressing by M512 and M536 and are representative of records from M514 and M533, respectively (not shown). The records are from sessions that had overall response rates most closely approximating the mean response rates shown in Figures 3 and 4 (see below). Acute effects of cocaine are illustrated in the leftmost panels. Under nondrug conditions, performance typical of that seen under FR schedules was observed; a pause after food presentation was followed by a high, constant rate (run) until the next presentation. For each monkey, pause length was longest during the large-ratio component (7.4 to 24.0 s across monkeys) and close to equivalent during the small- and medium-ratio components (0.8 to 11.8 s across monkeys). The highest baseline response rates and lowest reinforcement rates were maintained by the large-ratio contingencies for each of the monkeys and the lowest response (for 3 of the 4 monkeys) and highest reinforcement rates by the small-ratio contingencies (see Table 1).

For M536, performance following large doses of cocaine administered acutely was characterized by a very low response rate in the early portion of the session and then a gradual increase in rate. For M512, responding was suppressed in all components until the

Table 1

Mean number of food-pellet presentations per minute and per session across components as a function of acute and chronic administration of 1.0 mg/kg cocaine.

	Small[a]		Medium[a]		Large[a]	
	Pellets per minute	Pellets per session	Pellets per minute	Pellets per session	Pellets per minute	Pellets per session
M512						
Control[b]	4.6	15.0	3.5	15.0	1.8	15.0
Acute	2.0	7.5	0.6	10.1	0.1	5.0
Chronic	6.2	12.0	1.2	10.0	0.4	9.4
M514						
Control	7.3	15.0	5.3	15.0	1.0	15.0
Acute	3.7	10.0	0.6	7.7	0.2	7.7
Chronic	6.9	13.0	3.5	12.3	0.2	7.0
M536-C2						
Control	10.2	15.0	5.3	15.0	1.4	15.0
Acute	4.9	13.3	4.2	13.3	0.4	11.7
Chronic	10.4	13.5	2.4	11.8	0.0	1.5
M533						
Control	7.3	15.0	4.8	15.0	1.8	15.0
Acute	4.8	11.8	1.0	11.5	0.3	10.5
Chronic	34.2	15.0	3.3	15.0	1.3	15.0
M536-C1						
Control	10.2	15.0	5.3	15.0	1.4	15.0
Acute	4.9	13.3	4.2	13.3	0.4	11.7
Chronic	26.7	15.0	8.0	15.0	1.6	15.0

[a] Ratio size.
[b] No drug.

last third of the session. Responding began abruptly and was characterized by very long pauses (average 61.9 s) or disrupted patterns during runs in the large-ratio component. This differential sensitivity to cocaine is illustrated most clearly in the record from the session preceded by an acute injection of 1.3 mg/kg. Once responding began, ratios were completed rapidly in the FR 5 (event pen up) and the FR 17 (event pen down) components, but only one ratio was completed in the FR 60 component (event pen alternately up and down).

In Figures 3 and 4, filled circles depict overall average response rates in each component as a function of dose of acutely administered cocaine. Cocaine produced dose-dependent decreases in overall response rates in each of the components for each of the monkeys; large doses (1.0 and 1.3 mg/kg) produced the largest decreases. For all 4 monkeys following the largest doses, response rates were reduced to approximately 40% to 57% of control rates in the small-ratio component and to approximately 8% to 12% of control rates in the medium- and large-ratio components. Reinforcement rates were similarly reduced by these doses: to 50% to 75% of control rates in the small-ratio components and to 1% to 30% of control rates in the large-ratio components (see Table 1). The total number of reinforcers obtained per session decreased, on average, 50% for M512 and M514 and 20% for M536 and M533, relative to the nondrug control.

Chronic Drug Effects

The effects of daily administration of 1.0 mg/kg cocaine can be divided into two categories: (a) the monkeys either ate the food pellets that were delivered contingent upon completion of ratios or (b) they did not eat the pellets. M512 and M514 always ate the pellets during the session. M536 stopped eating the pellets on the 4th day of chronic administration; this portion of the phase will be referred to as the Chronic 1 phase. After 91 consecutive days of drug administration (Chronic 1 phase), M536 started to eat the food pellets during the session and continued to do so for the remainder of the study. This portion of the phase will be referred to as the Chronic 2 phase. M533

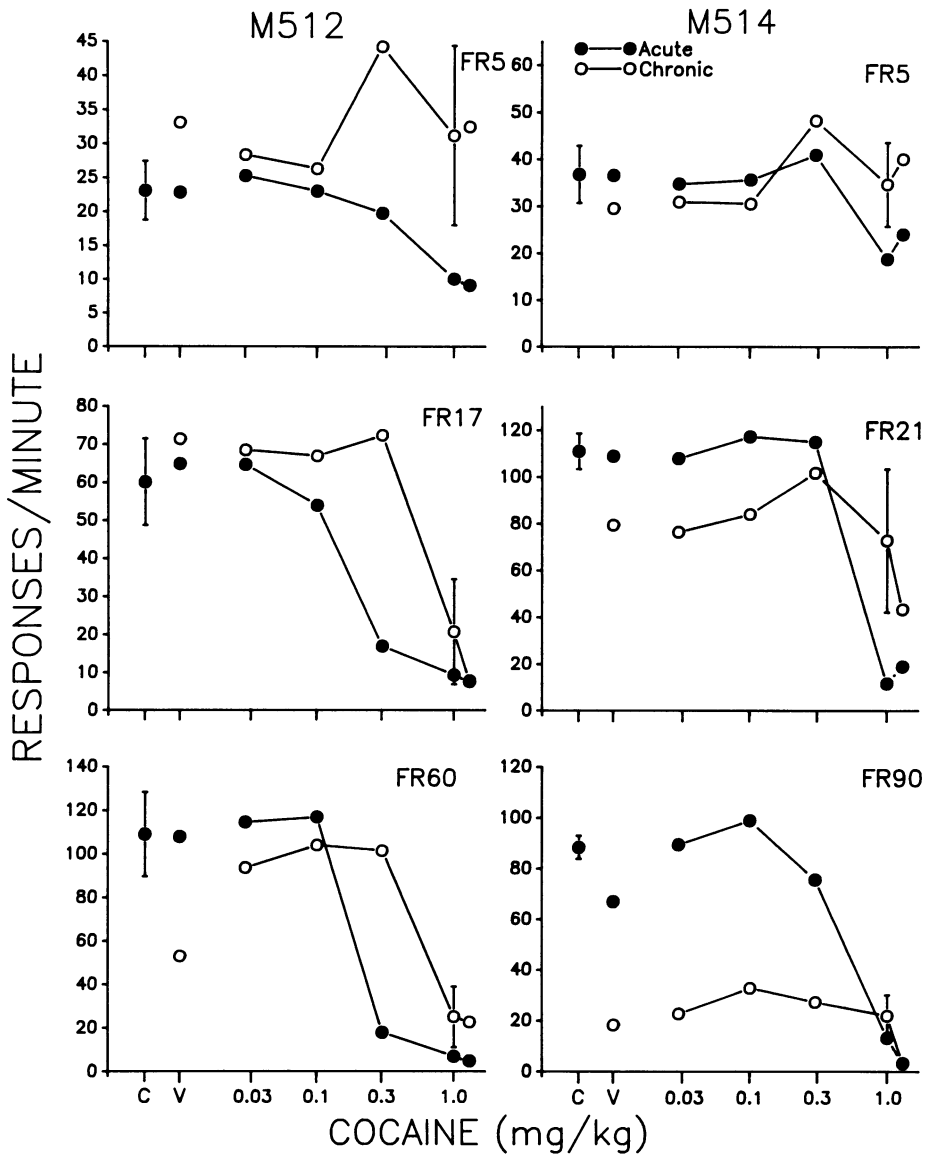

Fig. 3. Mean overall response rates as a function of the dose of cocaine for M512 (left panels) and M514 (right panels) during the small-ratio component (top row), medium-ratio component (middle row), and large-ratio component (bottom row). Points above C are means from sessions immediately preceding injections of a dose of cocaine or saline during assessment of acute effects. Points above V are means from sessions when saline was administered. The rightmost points on the curves are means from sessions when 1.3 mg/kg cocaine was administered. All points, except those above C and 1.0 during repeated administration, are means of at least two determinations. Open circles above 1.0 are means from all sessions that immediately preceded probes during assessment of effects during daily administration of 1.0 mg/kg. Bars on points above C and 1.0 mg/kg represent 95% confidence intervals of the mean. Note that the scales on the *y* axes differ.

always failed to eat the food pellets starting on the 7th day and continued throughout the 184 days of daily administration of 1.0 mg/kg cocaine.

Effects when pellets were eaten. In Figures 3 and 4, open circles and open triangles (M536-Chronic 2 phase) depict overall average response rates during chronic administration of 1.0 mg/kg cocaine. Responding returned to near-baseline levels during repeated drug administration; the magnitude of the recovery depended on the FR value. For each of the

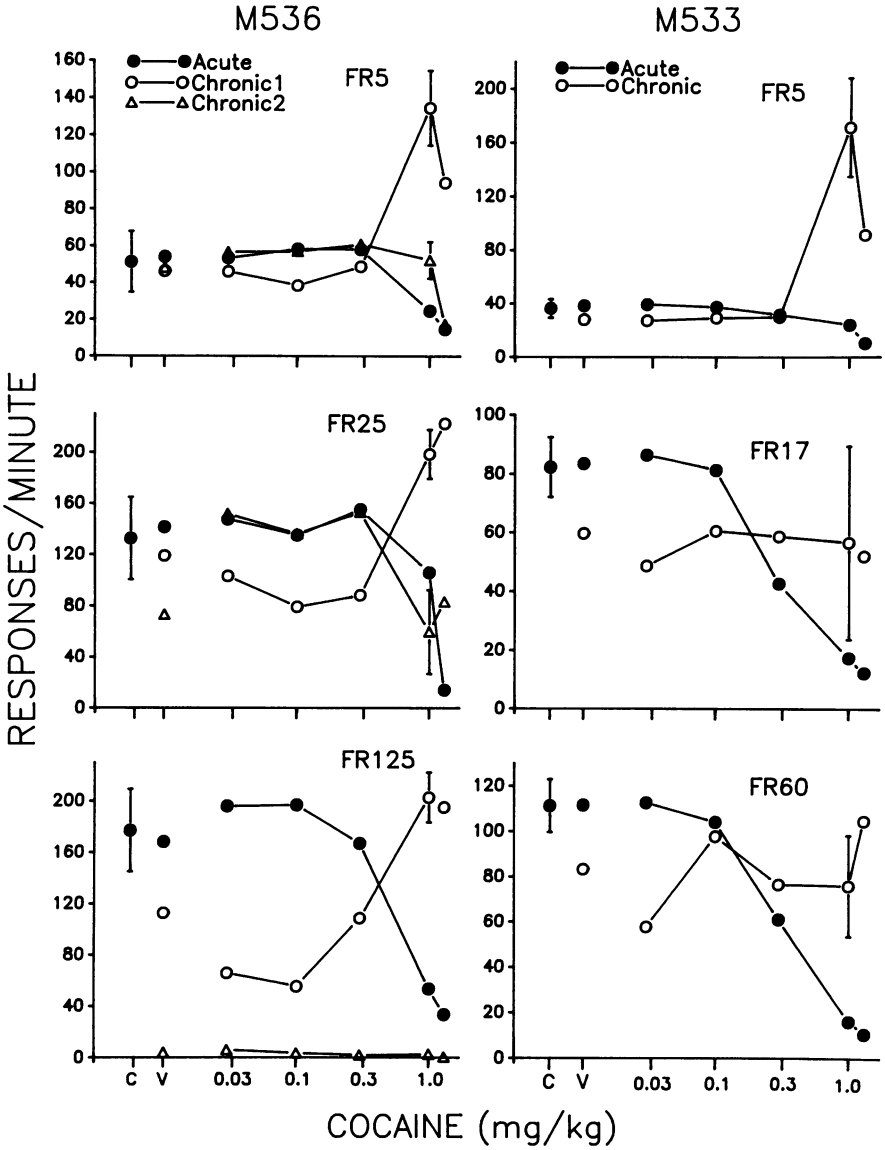

Fig. 4. Mean overall response rates as a function of the dose of cocaine for M536 (left panels) and M533 (right panels). Plotting conventions are the same as in Figure 3. For M536, open circles are means of administrations from the Chronic 1 phase and open triangles are means of administrations from the Chronic 2 phase. (See text for a description of the Chronic 1 and Chronic 2 phases.)

monkeys that ate the pellets (M512 and M514, Figure 3; M536, Figure 4) the rate-decreasing effects of 1.0 and 1.3 mg/kg cocaine were attenuated completely in the small-ratio component as response rates returned to or exceeded nondrug control rates (except M536-Chronic 2 phase at 1.3 mg/kg). Response-rate decreases in the medium- and large-ratio components were attenuated (the exception is M512 at 1.3 mg/kg in the medium-ratio component), but to a much smaller degree than under the small-ratio component.

As a consequence, reinforcement rate also increased during the small-ratio component and to a smaller degree during the medium- and large-ratio components. For M512 the number of reinforcers obtained per session increased by 30% in the small- and large-ratio

components, but did not increase in the medium-ratio component. For M514 the number of obtained reinforcers increased by approximately 25% or more in the small- and medium-ratio components, but similar to M536-Chronic 2, there was no increase in the large-ratio component. For M536-Chronic 2, the number of obtained reinforcers decreased relative to the number obtained under acute administration of 1.0 mg/kg in the medium-ratio component and, to a larger extent (from 78% to 10% of nondrug control), in the large-ratio component (see Table 1). Response rates during the large-ratio component for M514 and M536 were below the rates produced by acute administration of cocaine at most doses. This effect can be seen clearly in the right panels of the cumulative records in Figure 2 for M536 during the Chronic 2 phase. For this monkey, lever pressing usually ceased and usually remained so when the FR 125 component (event pen alternately up and down) was in effect.

Effects when pellets were not eaten. M536-Chronic 1 and M533 (Figure 4, open circles) usually left uneaten 40 to 45 of a possible 45 pellets per session when 1.0 or 1.3 mg/kg cocaine was administered. Overall response rates and food-pellet presentation rates were elevated to or above control rates in each of the components for M536 and in the small- and large-ratio components for M533. In the small-ratio component, response rates increased as much as 500% to 700% above the rates after acute administration of 1.0 and 1.3 mg/kg cocaine. These high rates are illustrated in the cumulative record for M536 after administration of 1.0 mg/kg (Figure 2). The session length was shorter, and responding was characterized by very short pauses after food delivery (pauses decreased approximately 70% during the large-ratio component), as illustrated in the record by straight lines. When the vehicle (saline) and doses less than 1.0 mg/kg were administered, both monkeys ate all the pellets, and response rates during the two larger ratio components often were lower than rates during acute drug administration. As illustrated in the cumulative record for M536 (Figure 2), the effects of administration of 0.3 mg/kg were a general decrease in response rates in the large-ratio component across the session instead of an initial disruption followed by recovery in rates after acute administration. The cumulative records for M536 (Figure 2) also show longer postreinforcement pauses (on average 253.4 s) and disruptions during the runs of the large ratios following saline administration. For M533, however, response rates after saline administration were comparable to the rates observed under 1.0 mg/kg, the chronic dose.

Time-Course Effects

Figures 5 and 6 display overall response rate as a function of dose of cocaine for each FR component, across blocks of the session for M512 and M536, respectively, and are representative of responding of M514 and M533, respectively. Recall that each block consisted of one presentation of each component and may be thought of as occurring in the first, second, and last third of the session.

For each monkey, the acute rate-decreasing effects of large doses of cocaine were attenuated across blocks (i.e., as the session progressed). Response rates generally recovered to control levels sooner in the session in the small- and medium-ratio components (e.g., in the second block for M536 and in the third block for M512) than in the large-ratio component (e.g., in the third block for M536 and not at all for M512). M536 showed increases above control levels late in the session under the higher ratio values (see FR 125, 0.3 mg/kg).

During repeated administration, for the monkeys that ate the pellets delivered contingent upon responding, a greater degree of tolerance was observed in the small-ratio component than during larger ratios in the first block of the session (Figures 5 and 6). As the session progressed, tolerance was evident in the medium- and large-ratio components. For the monkeys that did not eat the pellets, rates were elevated comparably across blocks of the session (Figure 6). Interestingly, response-rate decreases in the large-ratio component (compared to levels after 1.0 mg/kg cocaine) following administration of saline and cocaine doses smaller than 1.0 mg/kg grew larger across blocks of the session for M536 (Figure 6). This was also true for M514 (not shown).

Effects of terminating repeated administration. Figure 7 shows overall response rates, expressed as a percentage of nondrug control level, when saline was administered every day at the conclusion of the chronic drug administration. Rates shown are averages across 5-day blocks following cessation of daily cocaine administration. For M512, responding

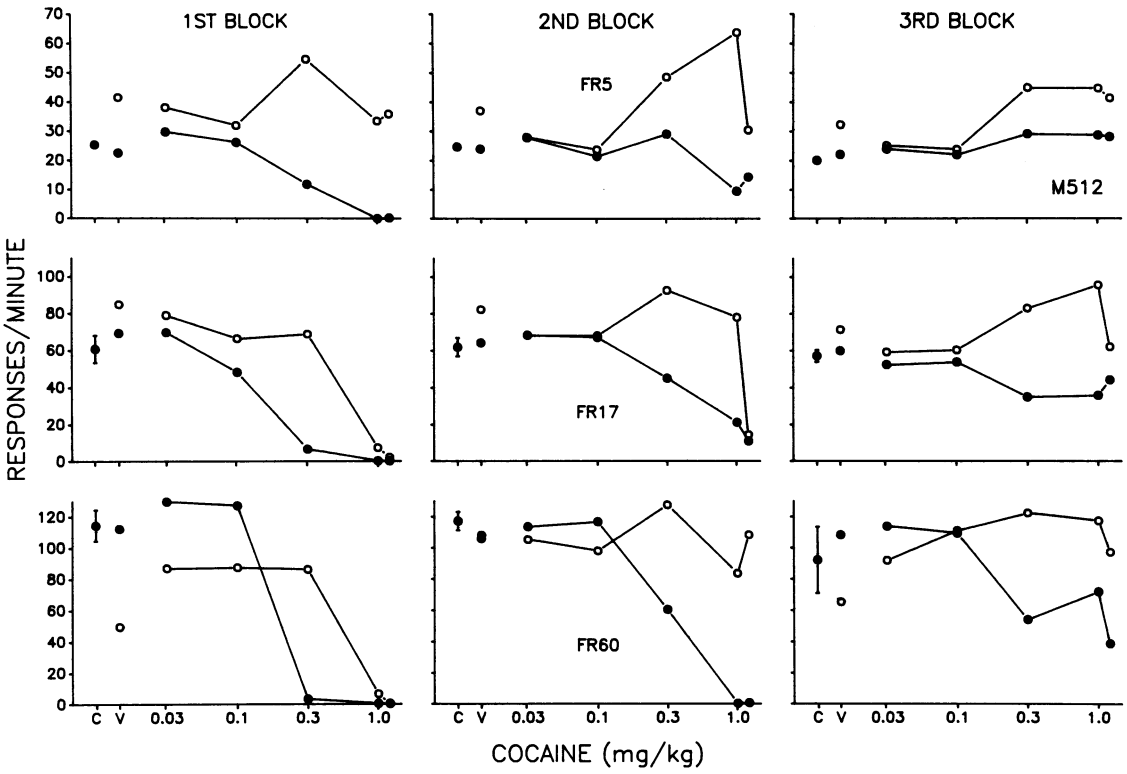

Fig. 5. Mean overall response rates as a function of the dose of cocaine for M512 across blocks of the session (columns) for each ratio component (rows). Plotting conventions are the same as in Figure 3. Filled circles are means from acute administrations, and open circles are means from administrations during daily 1.0-mg/kg cocaine administrations.

during the large-ratio component recovered to control levels during the first 5 days of daily saline administration. Recall that for this monkey, substitution of saline for the daily dose of cocaine reduced response rate in the large-ratio component to about 50% of control (Figure 3). For M514, responding during the large-ratio component recovered from 15% of control to about 60% of the control level after Days 22 to 26 of saline administration. Responding remained at this level for the next 12 sessions, at which time the experiment was terminated. For M536, during 10 daily saline administrations, response rates during the large-ratio component did not change appreciably from the preceding Chronic 2 phase (i.e., they remained very low). After saline injections were terminated, responding recovered to 80% of control level by Days 61 to 65 after the last cocaine injection, at which time the experiment was terminated.

The data for M533 are not included in Figure 7 because near the end of daily cocaine administration several manipulations were carried out in attempts to identify variables responsible for the maintenance of lever pressing despite the nonconsumption of the food pellets. Some of these manipulations included the administration of saline prior to sessions in which the feeder was disconnected. Consequently, unambiguous data concerning the withdrawal of daily cocaine were not collected for this subject.

DISCUSSION

Acute administration of cocaine produced dose-dependent decreases in overall response rates, and consequently in reinforcement frequency, in each of the ratio components. The performance maintained under the large-ratio contingencies tended to be more sensitive to cocaine in that lower doses frequently decreased rates in these schedules. Following re-

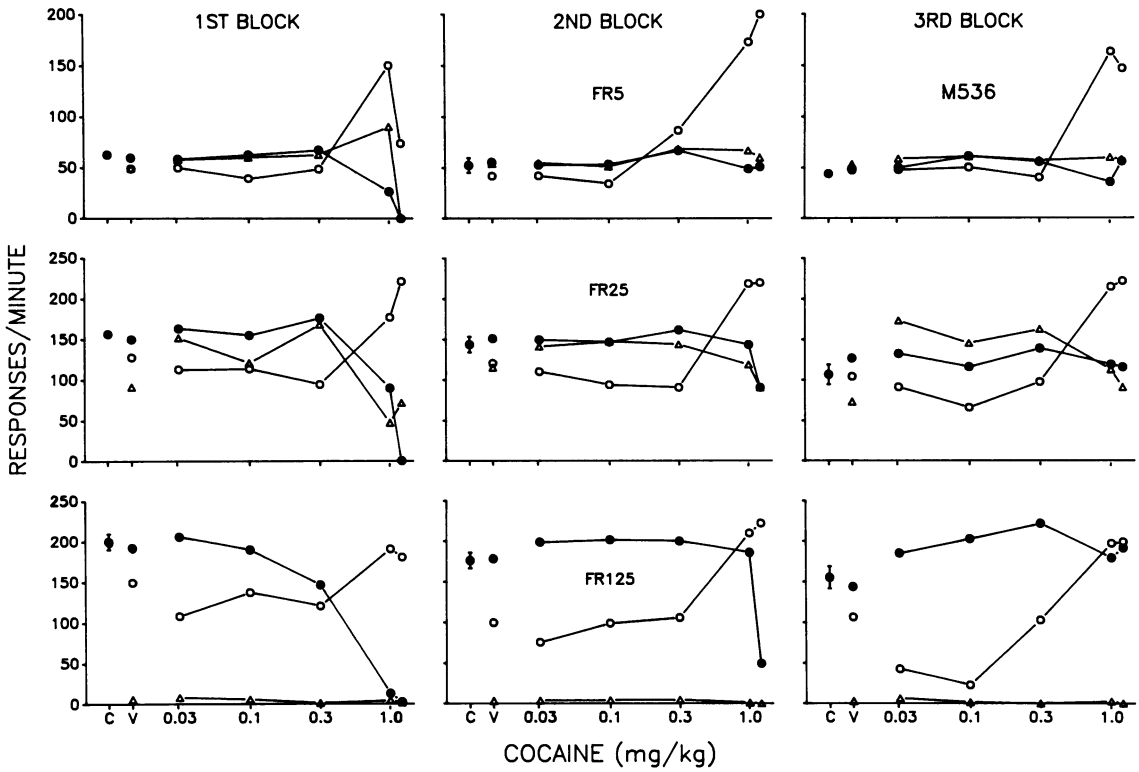

Fig. 6. Mean overall response rates as a function of the dose of cocaine for M536 across blocks of the session (columns) for each ratio component (rows). Plotting conventions are the same as in Figure 5, except that open circles are means of administrations from the Chronic 1 phase, and open triangles are means of administrations from the Chronic 2 phase.

peated administration of a dose that decreased response rates in all three components, tolerance usually developed to the rate-decreasing effects under each of the ratio contingencies. The degree of tolerance and when in the session it was first observed were dependent on ratio size. For example, for M512 (at 1.0 and 1.3 mg/kg) and M514 (1.3 mg/kg), performance returned fully to control levels during the small-ratio component only. For M533 and M536 during the Chronic 1 phase, performance returned to control levels or above in all the components, with the greatest degree of change in response rates occurring in the small-ratio component. Recall, however, that these changes in rate under larger doses occurred when the monkeys did not eat the pellets when they were delivered. During the Chronic 2 phase for M536 (when he consumed the food pellets during the session), tolerance was most pronounced in the small-ratio component at the chronically administered dose of 1.0 mg/kg.

Because cocaine's acute effects diminished across the session, with very little decrease in response rates during the third block, the time course of the drug's action in this situation was shorter than the session time limit. It is, therefore, illustrative to examine the effects during the first block of the session, when the acute effects were the greatest (see Figures 5 and 6). For all subjects, responding during repeated administration returned to control rates during the first block of the session only in the small-ratio component following administration of 1.3 mg/kg cocaine (1.0 mg/kg for M536). That is, during the time in a session that cocaine had its maximum effect, tolerance developed only in the small-ratio component. The results of the present study are therefore consistent with the results of the Hoffman et al. (1987) study, in which tolerance to cocaine's effects developed more fully under small FRs, and extend the generality of their findings to a different species, squirrel monkeys.

Hoffman et al. (1987) pointed to the ratio

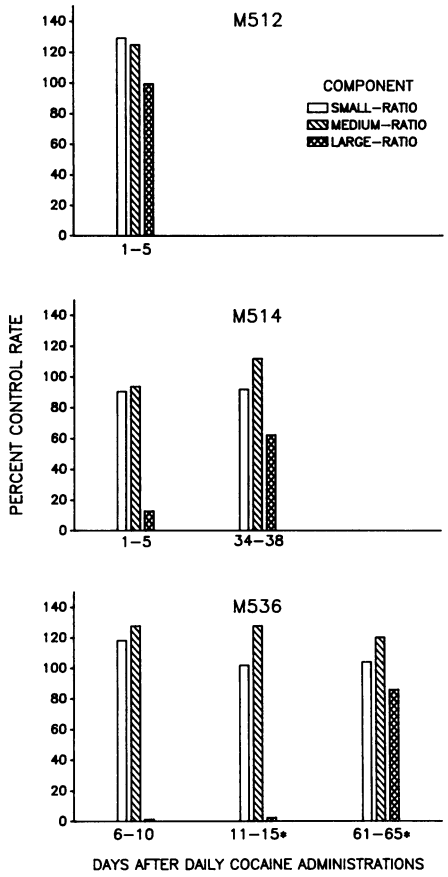

Fig. 7. Mean overall response rates, expressed as a percentage of control rates, as a function of number of days after termination of daily cocaine administrations during each type of component for M512 (top row), M514 (middle row), and M536 (bottom row). An asterisk indicates that no injections preceded the sessions indicated. Otherwise, saline was administered prior to sessions.

of responses per reinforcer as a modulator in the development of tolerance. The present results support this view, in that tolerance developed earlier in the session when the response requirement was low (i.e., FR 5). Unlike their study, however, in which 2 of 3 subjects showed no evidence of tolerance in the large-ratio component, the majority of subjects in this experiment showed some degree of tolerance during each of the components. This difference may indicate that the large ratio values in this experiment may not have been functionally as large as the values used in the Hoffman et al. study.

In the present study, control response rates were lowest in the small-ratio component and, generally, highest in the large-ratio component (for M514 the highest response rates were in the medium-ratio component). These rate differences could have contributed to the differential development of tolerance in the small-ratio component; that is, tolerance was more likely to develop when baseline rates were low. It has been shown that baseline response rates can be a determinant of drug effects, including those of "stimulants" (see Dews & Wenger, 1977, for a review). In the Hoffman et al. (1987) study, however, tolerance developed more completely in the small-ratio component, which had high control response rates, and did not develop, or developed to a much lesser degree, in the large-ratio component, which had the lowest control rates. Therefore, if there is a role for baseline response rates in the development of tolerance to cocaine, the relationship must be different for pigeons and monkeys.

For many behaviorally active drugs, development of tolerance to behavioral effects depends on the initial effect of reducing reinforcement frequency (Corfield-Sumner & Stolerman, 1978; Goudie & Demellweek, 1986; Schuster, Dockens, & Woods, 1966). Such findings have led to the formulation of the reinforcement-density or reinforcement-loss hypothesis, which states that, other things being equal, tolerance will be more likely to develop, or will develop more rapidly, to a drug's behavioral effects if those effects include a reduction in reinforcement frequency. This view was not completely supported in this experiment. Although there was reinforcement loss (both in number of reinforcers obtained and in rate of reinforcement) in each of the components early in the session, tolerance developed only in the small-ratio component. These findings support the suggestion of Hoffman et al. (1987) that reinforcement loss may be a necessary but not sufficient condition for the development of tolerance to cocaine's effects on schedule-controlled behavior.

Schama and Branch (1989) directly investigated the role of baseline reinforcement rates on the development of tolerance to the effects of cocaine. Key pecking by pigeons was maintained by a three-component multiple FI schedule of food presentation (5 s, 30 s, 120 s). FI schedules require only one response per reinforcer, independent of the interval value, and reinforcement rates depend largely on the

interval value; that is, response rates may vary widely yet have little effect on reinforcement rate. The FI values were selected to produce baseline reinforcement rates comparable to those in the Hoffman et al. (1987) study. Tolerance was observed under each FI schedule. That is, rate of reinforcement did not modulate how or whether tolerance developed. These results suggest that the response requirement per reinforcer is crucial in the differential development of tolerance observed in the present study and that of Hoffman et al., and that baseline reinforcement rates are less important.

Smith (1986) suggested that the development of tolerance could be influenced by the "global" density of reinforcement; that is, tolerance develops in a situation in which there was an initial greater loss of reinforcement. He demonstrated that tolerance to *d*-amphetamine's rate-decreasing effects differentially developed in the random-ratio (RR) component of a multiple RR differential reinforcement of low rate (DRL) schedule. When the RR component was removed from the schedule, and therefore all reinforcement was obtained via the DRL schedule, tolerance developed to the rate-increasing effects of *d*-amphetamine. In the present experiment, rate and number of obtained food presentations decreased proportionally most during the large-ratio component when 1.0 mg/kg was administered acutely for each of the monkeys (see Table 1). Contrary to Smith's results, tolerance was evident to a smaller degree and later in the session in the large-ratio component for the 3 monkeys who consumed the food pellets, despite the "greater loss" of reinforcement.

In the present experiment, number of reinforcers was held constant across components; therefore, component durations were a function of the ratio requirement. That is, the monkeys spent much less time in the small-ratio component compared to the large-ratio component. Because component duration can play a role in the determination of some behavioral processes (e.g., contrast: de Rose, 1986; McSweeney, 1982), the differential development of tolerance seen in the present study may to some degree depend on the component duration. Further research in which component durations are held constant would help resolve this issue.

The rate-decreasing acute effects of cocaine on FR performance in this study are consistent with the literature on effects with nonhuman primates (e.g., Gonzalez & Goldberg, 1977; Spealman et al., 1977, 1979) as well as with pigeons (Branch & Dearing, 1982; Hoffman et al., 1987) and rats (Woolverton et al., 1978). These data extend the results to performance maintained under larger ratios than previously cited and to a context in which two other ratio values were present as parts of a multiple schedule. This finding is important because multiple-schedule context can be a powerful modulator of a drug's effects (e.g., McKearney & Barrett, 1975). That acutely administered cocaine results only in reductions in response rate under FR schedules seems, therefore, to be a very general phenomenon.

In addition, these data contribute to the small body of literature on the behavioral mechanisms of tolerance to cocaine in nonhuman primates. Branch and Sizemore (1988) found that tolerance developed to the rate- or accuracy-decreasing effects of cocaine of squirrel monkeys' completion of two- to five-response sequences. Congruent with their findings, tolerance consistently developed to the rate-decreasing effects of lever pressing in squirrel monkeys in the present study when the response requirement was FR 5.

In the present experiment, substitution of saline and lower doses of cocaine during daily administration of 1.0 mg/kg cocaine did not always result in nondrug control-level responding, although the response rates were equivalent to or greater than rates under the chronically administered dose. For 3 of the 4 monkeys (M512, M514, and M536 during the Chronic 2 phase), this disruption was observed only for performance under the larger ratios. Substitution of saline for the daily dose during repeated administration may be conceptualized as a probe for behavioral dependence or "withdrawal." Behavioral dependence is said to be in evidence when behavior is disrupted relative to the responding seen during chronic drug administration (Schuster & Thompson, 1969; Woolverton & Kleven, 1988). Because response rates when saline and lower doses of cocaine were administered were about the same as those under chronic drug, the present results (when pellets were eaten) cannot be characterized as illustrating behavioral dependence. They do, nevertheless, reveal an additional ef-

fect of repeated cocaine administration. When the chronic drug regimen was stopped and saline was administered chronically, responding returned to within the previous nondrug control range relatively quickly for M512 and slowly for M514 and M536 (see Figure 7). These residual suppressive effects of repeated exposure to cocaine are more like a "behavioral hangover," the severity of which was related to schedule parameter.

The data for M536-Chronic 1 and M533 may provide evidence of dependence. Responding did recover when pellets were not eaten, and substituting saline or smaller doses for the repeatedly given dose resulted in disruption (see especially Figure 6). Interpretation of these data as indicating behavioral dependence, however, is compromised by our lack of understanding of the variables responsible for maintenance of lever pressing in the absence of consumption of the putative reinforcer (but see discussion below).

The present results, then, indicate that whether residual suppressive effects, as well as tolerance, develop to cocaine's effects may depend on behavioral parameters. Interestingly, there was a clear dissociation between tolerance and the residual suppressive effects in these experiments. Tolerance developed more fully when small ratios were arranged, whereas the suppressive effects were observed when larger ratios were programmed.

The persistence of disruption of responding under the larger ratios appears to be inconsistent with results reported by Hoffman et al. (1987), Branch and Dearing (1982), and Branch and Sizemore (1988). They all observed complete recovery of control rates when saline was substituted for the chronic dose of cocaine during daily administration (they did not administer chronic saline at the end of the chronic phase). However, in the Branch and Sizemore study (the only one of the three in which squirrel monkeys were used), the number of responses required for reinforcement varied from seven to ten, and in the Branch and Dearing study (which utilized a different procedure) six responses were required for reinforcement. Given these low ratios of responses to reinforcement, the present results predict that residual effects would not be observed in circumstances like those arranged by Branch and Sizemore and Branch and Dearing.

One of the more puzzling outcomes in the present study was that 2 of the subjects (M533 and M536) stopped eating the pellets delivered contingent upon completion of ratios during daily administration of 1.0 mg/kg cocaine. Response rates, nevertheless, were maintained at or above control levels. That is, the monkeys continued to respond even though they did not consume the putative reinforcer. Also striking for these 2 subjects is the degree of consistency of drug effects (see Figure 6) during this time. One possible partial account is that cocaine produced an anorexic effect, and therefore the monkeys stopped eating. It has been demonstrated that acute administration of cocaine can decrease food intake (e.g., Bedford, Lovell, Turner, Elsohly, & Wilson, 1980) and that tolerance to these appetitive effects develops when cocaine is administered daily in rats (Wilson & Brenkert, 1978). From this, we expected both monkeys to start eating the pellets sometime into the chronic phase (i.e., for tolerance to develop to the "anorexic" effect). M536 did start eating the pellets after 91 sessions of daily administration of 1.0 mg/kg cocaine, but M533 did not eat the pellets for the entire duration of daily administration (184 days). Not eating the food pellets because of an anorexic effect of cocaine does not explain why both monkeys continued to press the lever throughout the session. Usually when variables that decrease eating are applied, food-reinforced responding declines (e.g., Clark, 1958; Willis, Van Hartesveldt, Loken, & Hall, 1974). Another fact arguing against some sort of general anorexia is that the monkeys, once removed from the enclosure, generally ate the pellets and the postsession biscuits.

Another possible explanation of the continued responding is that stimuli associated with food delivery (feeder operation, dimming of lights, and pellet dropping in dispenser) maintained behavior, even though pellets were not eaten. It has been suggested that cocaine enhances the efficacy of conditioned reinforcers. Goldberg, Spealman, and Kelleher (1979) found that presentation of stimuli associated with cocaine administration contingent on drug-seeking behavior increased that behavior. Beninger, Hanson, and Phillips (1981) also showed that acquisition of lever pressing in mice on a lever associated with a tone previously paired with presentation of food (conditioned reinforcer) was greater during ad-

ministration of large doses of cocaine (5.0 and 10.0 mg/kg) than during saline administration. It is plausible that for the monkeys in the present experiment, conditioned reinforcers were powerful enough to maintain responding in each of the components. This view, too, is problematic because the effectiveness of conditioned reinforcers depends on the effectiveness of the primary reinforcers with which they are associated (Ferster & Skinner, 1957, pp. 679–680; Malott, 1966; Myers, 1958). Therefore, we expected the response rates for both monkeys to decrease as the conditioned reinforcing efficacy of the stimuli decreased throughout the chronic phase. The effects of cocaine administered both acutely and chronically on behavior maintained by conditioned reinforcement need to be characterized further.

In summary, the results from the present experiment support the suggestions of Hoffman et al. (1987) that the response requirement per reinforcer is a modulator of the development of tolerance to cocaine's effects (when the requirement was low, tolerance developed) and extend the generality of their findings to a different species. Additionally, residual suppressive effects of cocaine were observed to be dependent on schedule parameter.

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